REMARKS

Applicants thank the Examiner for consideration of their response to the restriction requirement and election of a species for further examination. Applicants respectfully request that the Examiner consider the amendments and remarks herein.

Support for new claims 61 through 82 is found throughout the specification and claims. New claims 61 through 82 reflect methods of treating B cell malignancies using both V_H and V_L chimeric proteins that are produced in insect cells. Support for new claim 61 is found in particular at claims 1, 2, 4, 5, 6, and 11.

Applicants acknowledge the Examiner's withdrawal of the species requirement with respect to light chain constant region isotype, heavy chain constant region isotype, and the protein used to isolate the chimeric proteins. Applicant acknowledge that the Examiner has withdrawn claim 17 from further consideration; applicants reserve the right to pursue this subject matter in continuation or divisional applications.

The Examiner asserts that the title of the invention was not descriptive and requested a title that is more clearly descriptive of the invention to which the claims are directed. Applicants have amended the title as indicated on page 2 of this paper (amendment to the specification at page 1, lines 1 to 2). Applicants request withdrawal of the objection in view of the title as amended herein.

The Examiner has pointed out that the abstract is of undue length. Applicants request withdrawal of the objection in view of the abstract as amended herein (approximately 140 words).

The Examiner has located an embedded hyperlink on page 35 at line 19. Applicants have amended the specification to delete the hyperlink. Applicants request withdrawal of the objection in view of the amendment to the specification herein. At the Examiner's request, Applicants have also corrected minor mistakes in the specification and added trademark notations.

Rejections Under 35 U.S.C. § 112 first paragraph

The Examiner has rejected claims 1-16 and 18-33 under 35 U.S.C. § 112, first paragraph, as the Examiner alleges that the specification, while enabling for altering a B cell mediated pathology that is a non-Hodgkin's lymphoma by administering a chimeric protein comprising a V_H and V_L region associated with the B cell clone from the patient to be treated does not

reasonably provide enablement for altering other B cell mediated pathologies. The Examiner has further alleged in rejecting claims 1-16 and 18-33 that the specification does not reasonably provide enablement for altering a B cell lymphoma by administering a composition comprising a chimeric protein comprising only a V_H region or only a V_L region.

In contrast, the Examiner subsequently states at the top of page 4 of the office action that "the art recognized that the B cell mediated pathology of non-Hodgkin's lymphoma and certain other B cell malignancies could be altered by administering a composition comprising the VH+VL of the immunoglobulin expressed by the lymphoma conjugated to a carrier such as KLH." The present invention describes the use of this technology to treat non-Hodgkin's lymphoma and other B cell malignancies using chimeric proteins obtained from a patient's B cell malignancy. As the Examiner has brought to our attention, an ordinary artisan would realize that non-Hodgkin's lymphoma is just one form of B cell lymphoma, as evidenced by Chapter 139 of The Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, Seventeenth Edition, 1999, Merck Research Laboratories, Whitehouse Station, N.J., pages 955-962) (*See*, office action at bottom of page 4.). Therefore, one of skill in the art would be able without undue experimentation, to use the methods and compositions of the invention to alter B cell malignancies other than non-Hodgkin's lymphoma using chimeric proteins comprising a VH region and a VL region derived from a patient suffering from a B cell malignancy.

Applicants respectfully request that the Examiner withdraw the rejection as the new claims 61 through 82 reflect the combined use of both VH and VL domains in the claimed method of the invention to treat B cell mediated malignancies. Applicant reserves the right to pursue methods of treatment and compositions utilizing only VH domain or only a VL domain in a subsequent application.

Rejection Under 35 U.S.C. § 102 Based on the Denney Patent

The Examiner has rejected claims 1-2, 4-10, 15-16 and 32-33 under 35 U.S.C. 102(e) as being anticipated by the Denney patent (U.S. Patent No. 5,972,334) as evidenced by Chapter 139 of the Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, 17th ed., 1999, Merck Research Lab., Whitehorse Station, N.J., pages 955-962) (the "Merck Manual"). The Examiner states that Denney teaches methods of altering a B cell malignancy, including B cell lymphomas, by administering a composition comprising a multivalent vaccine. The Examiner points out that Denney does not explicitly state the inclusion of non-Hodgkin's lymphoma in the

group of B cell lymphomas, a hypothetical ordinary artisan would include non-Hodgkin's lymphoma in the group of B cell lymphomas. The Examiner supports her conclusion by citing to chapter 139 of the Merck Manual.

The Examiner further states that Denney teaches multivalent vaccines comprising the VH and VL variable regions corresponding to the patient's B cells. According to the Examiner, the multivalent vaccines are obtained by cloning the corresponding nucleic acid sequences and combining them with the constant regions of either the kappa or lambda constant regions for the VL or either the gamma 3 or gamma 4 constant region in the case of VH. The Examiner points out while Denney does not explicitly state that the constant regions are full length constant regions, but based on the primers of Table 1-3, the Examiner asserts that the variable regions are full length and the constant regions are human.

The Examiner further points out that Denney teaches conjugating their multivalent vaccine to KLH, and that the composition may be co-administered with a cytokine, such as GM-CSF.

Applicants respectfully submit that Denney does not teach or suggest that the Id protein should be produced in insect cells. The new claims 61 through 82 require that the method be carried out in insect cells. Therefore, the rejection no longer applies to these new claims and Applicants respectfully request that the Examiner withdraw the rejection.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-3, 10-14, 18 and 23-33 as being obvious under 35 U.S.C. 103(a) over Denney (U.S. Patent No. 5,972,334) as evidenced by Chapter 139 of the Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, 17th ed., 1999, Merck Research Lab., Whitehorse Station, N.J., pages 955-962) and Edelman et al. (WO 96/07740) as evidenced by the alleged English language version of WO 96/07740, U.S. Patent No. 6,312,690.

The Examiner states that Denney teaches methods of altering a B cell malignancy, including B cell lymphomas, by administering a composition comprising a composition comprising the V_H+V_L regions of a patient's B cell clone linked to V_L regions that are either kappa or lambda and V_H regions that are human gamma 3 or human gamma 4. The Examiner points out that while Denney does not explicitly state the inclusion of non-Hodgkin's lymphoma in the group of B cell lymphomas, a hypothetical ordinary artisan would include non-Hodgkin's lymphoma in the group of B cell lymphomas as evidenced by Chapter 139 of the Merck Manual.

The Examiner then alleges that, as taught by Denney, the V_H region could readily be linked to a gamma 1 constant region instead of a gamma 3 or gamma 4 constant region.

The Examiner further alleges that the chimeric protein could be produced by cloning in baculovirus, and that Edelman et al. teach that the expression of antibodies in baculoviruses because baculovirus permits expression of antibody without risk of viral contamination associated with isolation of antibody directly from cells of human origin, standardization of the production process, and a practically inexhaustible supply. The Examiner continues that Edelman et al. teach a method of cloning both the VH and VL regions in a vector with constant regions under control of different promoters, expressing the protein in insect cells and then isolating the protein. The Examiner further alleges that Edelman teaches that the VH region may be linked to any human constant region, including the gamma 1 constant region, and that VL may be joined to either a kappa or lambda constant region. Edelman further teaches that the heavy and light chain can be expressed from the same vector, and may be expressed in insect cells including the Sf9 cell line. The Examiner then concludes that it would have been obvious to an ordinary artisan at the time the invention was made to combine the method of treating a B cell lymphoma as taught by Denney with the use of insect cells to express the chimeric protein as taught by Edelman.

Applicants respectfully disagree with the Examiner's broad characterization of Edelman. Edelman discloses the production of a chimeric antibody obtained by using the highly characterized variable region of a monoclonal antibody, the D7C2 antibody clone specific for Rhesus D, attached to a human constant region in order to obtain a therapeutic antibody that binds Rhesus D. Edelman focuses on the mass production of large amounts of this known and highly characterized antibody for use as a therapeutic binding antibody. The Gold invention focuses on the rapid production of a chimeric Id protein for use as an immunogen, not a therapeutic binding antibody. This is a key feature of the Gold invention – the speed of the process eliminates the requirement for a bridging round of chemotherapy while waiting for the Id protein to be produced. This allows use of the present invention independent of chemotherapy. This feature and speed of the process is set forth in the Gold Declaration, attached.

Further, it is not at all clear from Edelman that one of skill in the art would select insect cell production for a therapeutic immunogen. In Dr. Uhr's declaration, he points out that an ordinary artisan would not be expected to select insect cells to produce an Id protein (See paragraph 11 of Dr. Uhr's declaration). An ordinary artisan would be deterred from using insect

cells by the difference in glycosylation pattern between mammalian cells and insect cells and its effect on stability as illustrated by Dr. Uhr's declaration and the article by Altmann et al. (See paragraph 11 and 13 of Dr. Uhr's declaration). This difference would make it impossible for one to predict whether an insect cell-produced protein would successfully serve as an immunogen (See paragraph 11 of Dr. Uhr's declaration). Further, an ordinary artisan contemplating producing any therapeutic protein in insect cells might be dissuaded by the anticipated difficulties in convincing the regulatory agencies to approve this novel means of producing therapeutic proteins (See paragraph 12 of Dr. Uhr's declaration). An ordinary artisan would thus have no reason to stray from tried and true mammalian cell production methods, such as CHO cells.

Applicants further respectfully traverse the Examiner's rejection for failure to provide a motive to combine the cited references. To establish a prima facie case of obviousness, the Examiner must satisfy at least two criteria: (1) some motivation or suggestion to modify or combine the cited references, and (2) a reasonable expectation of success in combining the references. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). The Examiner has failed to provide any specific reason to combine the references other than general comments that one skilled in the art would be motivated to combine the references or would be highly motivated to combine the references. The Federal Circuit has cautioned against obviousness arguments constructed by adding together two references without a specific suggestion to combine the references. In the 2002 case, In re Lee, the Federal Circuit revisited the standard for obviousness:

> The essential factual evidence on the issue of obviousness is set forth in Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966) and extensive ensuing precedent. The patent examination process centers on prior art and the analysis thereof. When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See, e.g.*, McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).
>
> "The factual inquiry whether to combine references must be thorough and searching." Id. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g.*, Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting C.R. Bard, Inc., v. M3 Systems,

> Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232(Fed. Cir. 1998)); In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617(Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("`teachings of references can be combined *only* if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

In re Lee, 277 F.3d 1338, 1342-43, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002).

Edelman teaches the production of the variable region of a monoclonal antibody, D7C2, cloned into a baculovirus expression vector. Denney teaches a method for immunization of a patient suffering from a B cell malignancy by using an Id protein derived from that B cell malignancy and produced in mammalian cells. The Examiner urges that an ordinary artisan would be motivated to combine the teachings, but the Examiner fails to provide any specific suggestion in either of the references to combine the immunization with an Id protein as taught by Denney with the antibody baculovirus expression system of Edelman. As illlustrated in Dr. Uhr's declaration, this is a surprising combination. The difference in glycosylation patterns might have proven to be an insurmountable problem.

The method of treatment taught by Denney is based on the use of a mammalian expression system to produce accurately processed and glycosylated Id proteins for use as an immunogen. One skilled in the art would expect the expression system of Denney to produce Id protein glycosylated in a mammalian fashion. One skilled in the art would not expect baculovirus cells to produce the same glycosylation as mammalian cells. Edelman does not teach the use of a protein produced in baculovirus as an immunogen, and thus one skilled in the art would not be able to predict their suitability as immunogens. As Dr. Uhr points out, one skilled in the art would not be motivated to combine the references; the unpredictability is too great (See paragraph 11 of Dr. Uhr's declaration). In the instant invention, the Applicants have demonstrated that an Id protein expressed in insect cells will successfully serve as an immunogen in treating a B cell pathology, as set forth in Dr. Gold's declaration. However, the success of the Applicants may not be used as a template used in hindsight to assemble references to formulate an obviousness rejections. ("Our case law makes clear that the best defense against the subtle

but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).)

In light of the above arguments, Applicants respectfully request that this rejection be withdrawn and claims 61 through 82 be allowed to issue.

Rejection Under U.S.C. § 103(a)

The Examiner has also rejected claims 19-22 as being obvious under 35 U.S.C. 103(a) over Denney (U.S. Patent No. 5,972,334) as evidenced by Chapter 139 of the Merck Manual of Diagnosis and Therapy (eds. Beers M.H. and Berkow R, 17th ed., 1999, Merck Research Lab., Whitehorse Station, N.J., pages 955-962) and Edelman et al. (WO 96/07740) as evidenced by the alleged English language version of WO 96/07740, U.S. Patent No. 6,312,690, and further in view of Tan et al. (Biotechnol. Appl. Biochem. 1999, 30:59-64) and Mroczkowski et al. (J Biol. Chem. 1994, 269:13522-28).

The Examiner relies on the argument summarized in the section above, and admits that Denney and Edelman do not teach the detailed components of the expression vector as set forth in claims 19, 20, 21, and 22. However, the Examiner characterizes the teaching of Tan as teaching the successful production and secretion of antibody light chain in insect cells using the honey bee melittin signal sequence. The Examiner further characterizes Mroczkowski as teaching the secretion of heterologous proteins with a baculovirus expression vector in insect cells using the human placental alkaline phosphatase signal sequence. As we have demonstrated above, it is not obvious to combine Denney and Edelman, and it is not obvious to focus on that hypothetical combination with the refinements taught by Mroczkowski and Tan. Taken individually, the narrow teachings of Mcroczkowski and Tan fail to suggest the Applicant's invention.

As demonstrated above in regard to the Examiner's other obviousness rejection, the Examiner has again selected references from the literature that provide individual elements of the Applicants invention. The Examiner has again relied on general assertions that one skilled in the art would combine these teachings, but has failed to provide any specific motivation or suggestion within these references that a skilled artisan should combine these elements. Thus, under the holding of In re Lee and In re Dembiczak as discussed above, the Examiner has failed

to establish a prima facie case of obviousness under 35 U.S.C. § 103(a) and the rejection should be withdrawn and claims 61 through 82 be allowed to issue.

CONCLUSION

It is believed that all claims are now in condition for allowance. Notification to that effect is respectfully requested. If it is believed that prosecution may be furthered thereby, the Examiner is invited to contact Applicant's undersigned representative to discuss the same.

Respectfully Submitted,

Date: December 15, 2003

Jeffrey W. Guise, Ph.D.
Reg. No. 34,613

Pillsbury Winthrop LLP
11682 Camino Real, Suite 200
San Diego, CA 92130
Phone: 619.234.000
Fax: 858.509.010